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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,686	06/28/2001	Olga Bandman	PC-0044 CIP	7340

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EXAMINER

O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	11

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)
	09/895,686	BANDMAN ET AL.
	Examin r	Art Unit
	Eileen O'Hara	1646

-- The MAILING DATE of this communication appears on the cover sheet with the c rrsp ndenc address --

Period for R plly

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 14 January 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) 7-12 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-6 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) 1-12 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4) Interview Summary (PTO-413) Paper No(s). _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

1. Claims 1-12 are pending in the instant application. Claims 1 and 2 have been amended as requested by Applicant in Paper Number 10, filed Jan. 14, 2003.

Claims 7-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claims 1-6 are currently under examination.

Priority

2. Applicants' amendment to the specification to update the priority in the first sentence is acknowledged.

Objection to Specification

3. The objection to the specification is withdrawn in view of Applicants' amendment.

Withdrawn Rejections

4. The rejection of claims under 112 § 2 is withdrawn in view of Applicants' amendment.

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous Office Action, Paper No. 9, at pages 3-6, and below.

Applicants traverse the rejection and assert that the Examiner has not met her burden of proof to provide evidence or sound scientific reasoning why one skilled in the art would have reason to doubt Applicants' assertion of utility, and that the utility requirement, according to established law, is not an onerous one. Applicants assert that to meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful" and confers a "specific benefit" on the public, and cite *Anderson v. Natta and Brenner v. Manson*. Applicants cite *Juicy Whip v. Orange Bang Inc.*, as support that the threshold of an invention being useful is not high, and cite *Stiftung v. Renishaw PLC*, in which the United States Court of Appeals for the Federal Circuit explained"

An invention need not be the best or only way to accomplish a certain result, and it need not only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility."

Applicants further submit that if the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific, and cite *Standard Oil Co. v. Montedison, S.p.a.*, and assert that the specificity requirement is met unless there the asserted utility amounts to a "nebulous expression" such as

“biological activity” or “biological properties” that does not convey meaningful information about the utility of what is being claimed (*Cross v. Iizuka*), and in addition to conferring a specific benefit on the public, the benefit must also be “substantial” (*Brenner*), and a “substantial” utility is a practical “real-world” utility (*Nelson v. Bowler*). Applicants also assert that once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it, and applicant need only prove a “substantial likelihood” of utility and that certainty is not required. Applicants assert that the Examiner has not presented any evidence or sound scientific reasoning why one skilled in the art would doubt Applicants’ identification of the disclosed polypeptide of SEQ ID NO: 1 as a member of the subfamily of metabotropic GPCRs having a well-established utility, and that in view of a well-established utility for the claimed invention based on this identification, the threshold for a specific and substantial utility is met automatically and the applicant need not make any showing to demonstrate utility.

Applicant’s arguments have been considered but are not persuasive. Although the protein of the instant invention may be a G-protein coupled receptor, it is not predictable what the function of any GPCR protein is from this information. Whereas a broad class of enzyme such as the ligases have a general utility in such an application as ligation of DNA for cloning purposes and which is essentially applicable to all of the members of that class, the class of proteins known as G protein-coupled receptors do not have a common practical utility which is based upon a property common to all of the members of that class. It is well known in the art that a certain class of dopamine receptor, for example, can be employed to identify agents useful in the treatment of Parkinson’s disease whereas other classes of dopamine receptors can not. It is also well known that a nucleic acid encoding a particular dopamine receptor can be employed to

identify individuals with a predisposition for alcoholism whereas a nucleic acid encoding any other dopamine receptor can not be employed in this capacity. Further, there is no support for an argument that identification of membership in the G protein-coupled receptor superfamily automatically confers a well-established utility, since members of this class bind to a large variety of different ligands and modulate vastly different physiological processes. Each GPCR receptor or receptor-like protein responds to different ligands, mediates different signals and produces different responses in different cell types, and it is not predictable what the specific physiological function of a GPCR is based on structure. In the minireview of Ji et al., The Journal of Biological Chemistry, Vol. 273, No. 28, July 1998, pages 17299-17302, it is taught that the G protein-coupled receptor superfamily contains nearly 2000 members, which have the same basic structure, but are divided into subfamilies that bind different types of ligands, such as the biogenic amine receptors, nucleoside and nucleotide receptors, eicosanoid receptors, glycoprotein hormone-releasing hormone receptors, glucagons, calcitonin, vasoactive intestinal peptide receptors, parathyroid hormone receptors, protease activated receptors, glycoprotein hormone receptors and neurotransmitter receptors. Though the protein of the instant invention may be classified as a member of the GPCR superfamily, this does not automatically confer a specific and substantial utility to the protein, since there is extreme diversity in the activities and biological functions of these receptors.

On page 1096 of the Utility Guidelines, third column, it is stated:

“For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class.”

The protein of the instant invention falls into this category.

Applicants further assert that, in addition, they have presented ample evidence for an asserted utility of the claimed polynucleotide of SEQ ID NO: 7 as diagnostic for cancer, in particular follicular carcinoma of the thyroid based on significant differential expression (4-fold) in that disease condition over that found in any other thyroid tissue examined, either normal or otherwise diseased. On page 10 of the response Applicants explain what the terms "Abundance" and "% Abundance" mean as to total transcript abundance and relative abundance, and assert that the finding of a 4-fold higher expression of this sequence in follicular carcinoma compared with any other thyroid tissues examined is highly significant and would provide a clear utility to one skilled in the art for the use of the polynucleotide in the detection and diagnosis of this condition in thyroid tissue. Applicants' also disagree with the Examiner's contention that the occurrence of this transcript in only a single library associated with follicular carcinoma is not sufficient to support its' use as a diagnostic indicator for this condition, and the fact that a number of thyroid libraries were examined representing both normal and diseased thyroid, and the only the library associated with follicular carcinoma showed a level of expression 4-fold higher than any other thyroid tissue clearly indicates that, more likely than not, the level of expression of the gene transcript in this tissue is associated with the disease condition. In addition, Applicants assert that the Sen reference teaches that in thyroid cancers in particular, the only reference to aneuploidy in follicular carcinomas suggests that "Genome wide screening of follicular thyroid tumors revealed frequent loss of chromosome 22 in widely invasive follicular carcinomas", and the only evidence of aneuploidy in follicular carcinomas would not account for

the increase expression of a gene associated with the disease as disclosed in the instant application.

Applicants' arguments have been fully considered but are not deemed persuasive. For example, use as a cancer diagnostic, as asserted by Applicants, would be a specific and substantial use of the polypeptide and/or nucleic acids if a correlation were found between the molecules of the invention and follicular carcinomas. However, the only correlation supporting the asserted utility is based on expression of the gene in one single library. Even if aneuploidy were not an issue in gene expression, this is not sufficient guidance to use the claimed polypeptides as a marker for diagnosis, detection or treatment of cancers. The determination of a cancer marker must be based on studying results from a considerable number of patients, and statistical analysis. For instance, the Guidelines for Marker Development by the National Cancer Institute (NCI) clearly indicate the data required to proceed, and the considerations for preliminary identification of a potentially useful marker in the initial step. Some of the considerations in the Guidelines are:

"Step 1: ... Can a patient *population* be defined for which this marker may have utility? What is an expected range for the prevalence of this marker in population of potential interest? The number of specimens that should be assessed at this stage will vary depending on the question asked or the intended use of the marker. If *prevalence is being assessed*, then >20 specimens should be examined so that a marker present in 5% of cases would have a reasonable chance of being detected in the set of specimens. The numbers to be assessed for other questions will depend on the statistical design, the difference that would be meaningful to detect. Estimate prevalence of the marker on an *expanded* collection of targeted specimens.

Step 5: ... The intended use should be more clearly defined and careful *statistical* designs applied to studies that usually have to include *large number of cases*."

For the obvious reason, none of the critical questions or considerations for the determination of a cancer marker above can be answered or met by the present application. As such, one skilled in the art would not have accepted the assertion that the polypeptide can be used as a specific marker for follicular thyroid cancer. Therefore the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6.2 Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO: 1. However, the claims as written include polypeptides comprising fragments and homologues, encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO: 1, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as

set forth in *Regents of the University of California v Eli Lilly & Co*, 119F3d 1559, 1569, 43

USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

“To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention”. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) (“[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.”) Thus, an applicant complies with the written description requirement “by describing the invention, with all its claimed limitations, not that which makes it obvious,” and by using “such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention.” Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the ‘525 patent, “requires a precise definition, such as by structure, formula, chemical name, or physical properties,” not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, “an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself.” Id at 1170, 25 USPQ2d at 1606.”

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO: 1. Protein function, however, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrogenesis whereas closely related TGF-beta family members-BMP-2

and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences. The instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polynucleotides encompassed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7.1 Claims 1 and 3-6 remain rejected under 35 U.S.C. 102(b) as being anticipated by Valenzuela et al., WO 99/55721, Nov. 4, 1999, for reasons of record in the previous Office Action, Paper No. 9, at pages 7-8.

Applicants traverse the rejection and assert that as the present application meets the requirements for 35 USC § 112, first paragraph, for the reasons above, the prior application meets those requirements and the requirements for claiming the benefit of the earlier application are met, and therefore, Valenzuela et al. do not anticipate the claims.

Applicants' arguments have been fully considered but are not deemed persuasive, as discussed above in the rejections under 35 USC § 101 and § 112.

7.2 Claims 1 and 3-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al., U.S. Published Application 20030055236, effective filing date June 17, 1999 (divisional of 09/334,595).

Claims 1 and 3-6 encompass an isolated cDNA comprising a nucleic acid encoding a fragment of SEQ ID NO: 1 from I51-V72, G88-V109, C116-A145, I156-L175, M207-P229 or G242-T264 of SEQ ID NO: 1, vector and host cell comprising the cDNA, method of using the cDNA to produce the encoded protein, and composition comprising the cDNA and a labeling moiety.

Moore et al. disclose a nucleic acid molecule (SEQ ID NO: 22) that encodes a protein (SEQ ID NO: 146) that is 100% identical to the polypeptide of SEQ ID NO: 1 from amino acids 1-384 of the instant application, and therefore discloses an isolated cDNA comprising a nucleic acid encoding a fragment of SEQ ID NO: 1 from I51-V72, G88-V109, C116-A145, I156-L175,

M207-P229 or G242-T264 of SEQ ID NO: 1. Moore et al. also teach vectors (claim 7), host cells (claims 9-10) method of producing protein (claim 15) and labeled DNA (paragraphs 1078, 1080 and 1238). Therefore, Moore et al. anticipates the claims.

It is believed that all pertinent arguments have been answered.

Conclusion

8. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner


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